**STANDARD PROTOCOL**

A multi-centre, randomized, double-blind, clinical trial to evaluate the safety and efficacy of herbal medicine compared to the standard of care for the treatment of hospitalized patients with mild to moderate cases of novel coronavirus disease (COVID-19).

EFFICACY

This protocol was developed based on the request from some Member States to the WHO for support in the clinical trials of herbal medicines developed in their countries for the management of COVID-19. As a response to the request from Member States to the WHO-AFRO this Protocol was developed for countries to adapt to conduct the clinical trials phase III depending on available information on the herbal medicine. This protocol has been developed following the structure of the WHO MASTER Protocol for the Solidarity Trials

Version number 4.0.

26th September 2020.

Developed by:

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TWAS Laureate in Medical Sciences.

Professor of Pharmacology**.**

**WHY DO WE NEED A STANDARD PROTOCOL?**

Some of the Member States of WHO-AFRO had contacted the WHO-AFRO for support *vis-à-vis* protocol development to clinically evaluate herbal products developed by their scientists for the treatment of COVID-19. Some of them sent their draft protocols for the study. Based on such requests, the WHO-AFRO appointed a Consultant to develop a Standard Protocol for the clinical evaluation of herbal medicines against coronavirus in the WHO African Region. This protocol is structured in accordance with the WHO Master Protocol for the Solidarity Triials. Subsequently, the WHO-AFRO and Africa Centre for Disease Control and Prevention (Africa-CDC; representing the African Union) partnered to jointly provide the support regarding the development of the Standard Protocol and subsequently oversee the management of the trial. It provides the basis for the standardization of protocols for the evaluation of herbal medicines against COVID-19 in the region.. It is a guide which Member States can adapt in compliance to their national regulations and prevailing practical realities. However, it is anticipated that the Standard Protocol will ensure consistency in the conduct of the clinical trials to generate credible evidence.. The results of the trial will be analysed by the Data Safety and Monitoring Board (DSMB). Thereafter, the DSMB will submit their recommendation to the Member States *vis-à-vis* clinical safety and efficacy of the herbal medicines. Thus, the Standard Protocol forms the basis for the scientific validity of the outcomes of the study, which then provides evidence whether or not the herbal medicine is safe and efficacious. Such clinical evidence is crucial to the recognition and acceptance of the outcomes of the study by the international scientific community. Furthermore, the proposed study will provide the basis for the registration or otherwise of the herbal medicine by the national medicine regulatory authority (NMRA).

**THE STATEMENT OF COMPLIANCE**

The study will be carried out in accordance with the following, as applicable:

* All National and Local Regulations and Guidance applicable at each site
* The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6(R2) Good Clinical Practice, and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research,
* National regulatory and ethical requirements.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol including statements regarding confidentiality, and according to local legal and regulatory requirements, and ICH E6 (R2) GCP guidelines.

|  |
| --- |
| Site Investigator’s Signature: |
| Signed: |  | Date: |  |
|  | NameTitle |  |  |

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## ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse Event |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| BP | Blood Pressure |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| CMS | Clinical Material Services |
| Cr | Creatinine |
| CRF | Case Report Form |
| CROMS | Clinical Research Operations and Management Support |
| CSR | Clinical Study Report |
| CQMP | Clinical Quality Management Plan |
| EC | Ethics Committee |
| USFDA | United States Food and Drug Administration |
| FWA | Federal Wide Assurance |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| Hgb | Haemoglobin |
| HR | Heart Rate |
| IB | Investigator’s Brochure |
| ICD | International Classification of Diseases |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| IV | Intravenous |
| MCG | Microgram |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MERS | Middle East Respiratory Syndrome |
| MOP | Manual of Procedures |
| N | Number (typically refers to subjects) |
| NDA | New Drug Application |
| OP | Oral pharyngeal |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PLT | Platelet |
| PP | Per Protocol |
| PT | Prothrombin Time |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SARS | Severe Acute Respiratory Syndrome |
| SDCC | Statistical and Data Coordinating Centre |
| SDSP | Study Data Standardization Plan |
| SMC | Safety Monitoring Committee |
| SNP | Single Nucleotide Polymorphisms |
| SOA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T. Bili | Total Bilirubin |
| UP | Unanticipated Problem |
| US | United States |
| WBCGACPGHPPGMPQAS | White Blood CellGood Agricultural Collection PracticesGood Herbal Processing PracticesGood Manufacturing PracticesQuality Assurance Systems |

**1.** **PROTOCOL SYNOPSIS**

**1.1** **Rational for the proposed clinical trial**

Presently, there is no effective medicine for the treatment of COVID-19. Beigel and his colleagues, on 22nd May 2020 published their findings on remdesvir[[1]](#footnote-1). Their report indicated that patients who received remdesivir had a shorter time to recovery than those who received placebo. The study defined recovery as being discharged from the hospital or being medically stable enough to be discharged from the hospital. The authors reported 7.1 % mortality rate in the remdesivir arm compared to 11.9% in the placebo arm. That was a very modest improvement observed among the very severe COVID-19 patients.

Furthermore, on 10th June, Oxford University, UK, released a statement on the clinical outcome of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) using dexamethasone (6 mg peroral or parental) daily[[2]](#footnote-2). The justification for the study is based on the understanding that coronavirus disease 2019 (COVID-19) is associated with diffuse lung damage. Corticosteroids may modulate immune-mediated lung injury and reduce progression to respiratory failure and death. It was an open label design which involved 2,104 study participants randomly allocated to receive dexamethasone for ten days compared with 4,321 study participants who were on standard of care. The primary outcome was 28 days mortality. The preliminary results indicated that dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (p=0.14). That is a very encouraging finding that dexamethasone can significantly reduce mortality in COVID -19 very severe patients. But dexamethasone lacked any effect on moderate to severe COVID-19 patients who constitute about 95% of the patients. Definitely, the search for effective treatment against COVID-19 must continue.

In the case of the herbal medicine (insert the code name), the preclinical studies show promising data on both efficacy and safety (insert summary of the preclinical data here). In case there is no empirical data on the herbal medicine, credible ethnomedical use for 25 years without any report of adverse effect will be accepted for the product to be subjected to controlled clinical trials In view of the emergency situation of COVID-19 in Africa and globally, it is prudent to subject the herbal product to clinical evaluation for safety and efficacy compared to the national standard of care. The study population will be those who have tested positive to COVID-19. Informed consent forms will be administered and consenting participants that meet the inclusion criteria will be recruited. The primary end-points of the study include:

* Development of or delay in the development or resolution of symptoms associated with COVID-19 or a significant reduction/complete clearance of Covid-19 virus.
* Degree of quality of life (Karnofsky Performance Scale).

The following are the secondary end-points:

* Significant changes in the biological markers of Covid-19 (e.g. haematological, cardiac, renal, hepatic, lung, immunological parameters).
* Development of drug-related toxicities sufficiently severe to warrant dose modification, interruption or permanent discontinuation.

Data analysis will use SPSS VERSION 26(IBM, ARMONK, NEW YORK, US). The calculated sample size for this study is 106 COVID-19 participants with mild to moderate symptoms. However, the exact sample size will be determined by the biostastician at the study site. The selection of the study participants will be based on inclusion and exclusion criteria of the study. The study protocol must be approved by the National Ethics Committee (NEC) for scientific merit while the National Medicine Regulatory Authority (NMRA) must approve the study for compliance with appropriate regulatory provisions. A Data Safety and Monitoring Board (DSMB) will be established by the study sponsor to monitor the safety and efficacy of the herbal medicine.

**1.2 Study design**

This study is a multi-centre, randomized, double-blind, clinical trial to evaluate the safety and efficacy of herbal medicine compared to the standard of care for the treatment of hospitalized patients with mild to moderate cases of novel coronavirus disease (COVID-19). The results in the Test Arm will be compared with those in the Control Arm who will receive the dommy (representing the herbal medicine but inactive) while they are on the national standard of care treatment. Assuming the participants on the standard of care are on three medications, they will get one dommy product in place of the herbal medicine. On the other hand, the Test Arm will receive the herbal medicine and three dommy products in place of the three medicines the participants on the Control Arm are using.

The treatment with the herbal medicine will be for 14 days of daily administration (insert dose schedule here). Depending on the known pharmacokinetic profile of the product or ethnomedical data, the dose schedule will vary appropriately. However, participants who are not clinically cured by Day 14 but improving will be given the herbal medicine for 28 days. All study participants will undergo pre-trial tests and also during treatment on days 1, 3, 5, 7 and 14. The tests include heart, lung, kidney and liver functions, complete blood count and PCR assessment of viral load. Every study subject will be required to abide by weekly follow up visits for one month initially after cure. Thereafter, the follow up visits will be monthly for six months which can be via phone or physical attendance at the study site. Since it is a phase III trial at each study site, the sample size for the study will be calculated by the biostatistician at the trial site targeting 95% confidence level. . The sample size calculation should take cognizance of those study participants who may die during the study period or withdraw before the conclusion of the study. Addtion of 10% to the calculated sample size is recommended. If the research team decides to undertake a phase II trial due to the available data, the biostatistician will calculate the exact sample size accordingly. The participants will be equally randomized to treatment and control arms.. Based on the continuous recruitment approach, the study may last for six months.

Randomization will be stratified by:

* Site
	+ Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

**1.3 Objectives**

**1.3.1 Primary objective**

The overall objective of the study is to evaluate the clinical efficacy and safety of the herbal medicine in comparison to the control arm on standard of care treatment in participants with mild to moderate cases of COVID-19.

* Quantitative SARS-CoV-2 virus in blood at days 3, 5, 7, 14 and 28
* Percent of study participants with SARS-CoV-2 detectable in oropharyngeal (OP) sample at days 3, 5, 7, 14 and 28.
* Quantitative SARS-CoV-2 virus in OP sample at days 3, 5, 7, 14 and 28.

Due to variabilities of viral clearance among individuals as well as responses to the herbal medicine,. tests on Day 28 will be necessary. If the viral clearance occurs earlier than Day 28, the testing will stop accordingly since

#### 1.3.2 Secondary Objectives

###### *Clinical Severity*

*Ordinal scale:*

* + - Time to an improvement of one category from admission on an ordinal scale.
		- Participant clinical status on an ordinal scale at days 3, 5, 7, 14 and 28
		- Mean change in the ranking on an ordinal scale from baseline to days 3, 5, 7, 14 and 28 from baseline.

###### *Hospitalization*:

###### Usually study participants with mild to moderate symptons of COVIUD-19 do not require hospitalization. However, in order to secure effective compliance with the provisions of this protocol, all study participants will be hospitailized.

* + - Estimated duration of hospitalization is 14 days. However, the Principal Investigator (PI) will decide based on the progress of each study participant regarding the duration of hospital stay.

Evaluate the safety of the intervention and viral clearance (as indicated above) through 28 days (weekly visit after discharge) and subsequently monthly for 6 months of follow-up as compared to the control arm as assessed by:

* Cumulative incidence of serious adverse events (SAEs)
* Cumulative incidence of Grade 3 and 4 adverse events (AEs).
* Discontinuation or temporary suspension of infusions (for any reason).
* Statistically significant changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST for duration of drug administration..

### **1.4 Study Endpoints**

#### 1.4.1 Primary End-point

* Significant reduction (eg 50%) or complete clearance of SARS-CoV-2 virus in the OP samples. on Day 14.

**1.4.2 Secondary End-points**

* Significant changes in the biological markers of COVID-19 (e.g. haematological, cardiac, renal, hepatic, lung, immunological parameters).
* Status on an ordinal scale assessed daily while hospitalized and on day 14 or any other scale of assessment familiar to the reserachers.
* Duration of hospitalization .
* Date and cause of death (if applicable).
* Grade 3 and 4 adverse events (if applicable)
* SAEs.
* White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on days 1; 3, 5, 7 and 14 (while hospitalized, if applicable); 28 (if able to return to clinic or still hospitalized).

### **1.5 Inclusion Criteria**

* Participant (or legally authorized representative) provides written informed consent prior to initiation of any study procedures. Procedures for obtaining informed consent are contained in the Investigator’s Brochure and the Standard Operating Procedures (SOPs)
* Understands and agrees to comply with planned study procedures.
* Agrees to the collection of OP swabs and venous blood samples as per this protocol.
* Male or non-pregnant female (pregnancy test) adult ≥18 years of age at time of enrolment.
* Laboratory-confirmed SARS-CoV-2 infection as determined by PCR at a Government approved lab. from throat/nasopharyngeal swab.
* Illness of any duration, and at least one of the following:
* Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or
* Clinical assessment (evidence of rales/crackles on exam)
* Creatinine ≤ 110 umol/L, creatinine clearance rate (EGFR) ≥ 60 ml / min / 1.73m2, AST and ALT ≤ 5 × ULN, TBIL ≤ 2 × ULN;
* A Normal ECG Baseline result, which is maintained throughout the study.

 **1.6 Exclusion criteria**

Participants with the following conditions will be excluded from the study:

* ALT/AST > 2 times the upper limit of normal.
* Pregnancy (pregnancy test) or breast feeding.
* Anticipated transfer to another hospital which is not a study site within 72 hours.
* Allergy to any study medication or allergies to artemisinin containing products
* Shortness of breath
* Known prolonged QT syndrome
* Use of concomitant medications that prolong the QT/QTc interval
* Co-morbidity with other viral pneumonia
* Patients on immunomodulators
* Participants who in the opinion of the investigators after assessing all relevant parameters are unsuitable for the study.

###

### **1.7 Study Population**

### Adult (≥18 years old) male and female participants with COVID-19. In most African countries the official age of adulthood is 18 years.

### **1.8 Sites**

The potential site will be IRB/NMRA approved by the relevant National Ethics Committee (NEC) and NMRA after which the processes for the recruitment of participants can commence. Among others, the NEC/IRB/NMRA will determine suitability of a site regarding qualified personnel who have relevant experience in clinical trials with the discipline to adhere to protocol provisions and appropriate health infrastructure. Once a potential site has been identified and approved by the national EC//NMRA, the Regional Advisory Expert Committee (REAC) will be given the report together with the curriculum vitae of the study team.. Thereafter, if the report of the inspection is positive, site training will be undertaken by the REAC. The DSMB will be involved in monitoring the study for safety and efficacy while the NMRA will exercise its oversight regulatory monitoring.

### **1.9 Study intervention**

The goal of the study is to assess the safety and efficacy of the herbal medicine for the management of COVID-19 and compare to the standard of care. It is a comparator study. The study has two arms; the Test Arm will be administered herbal medicine while the Control Arm will be given the dommy product (in place of the herbal medicine) together with the national standard of care treatment for the country. Since it is a double-blind study, both arms will receive the same number of medicines only that the Control Arm will be given the standard of care treatment while the Test Arm will use the herbal medicine plus dommy products (inactive) which will match the medicines given to the psarticipants on the Control Arm. All study participants will be randomized through an appropriate computer application to receive either herbal medicine or the dommy product (plus national standard of care treatment) Both medicines and the dommy prodtcs will be matched for colour, taste, route of administration and dose sequence. The study will randomize participants 1:1 to dommy product (plus national standard of care treatment) or herbal medicine. The dommy product will be exactly as the herbal medicine except that it will lack the active ingredients.

### **1.10 Study Duration**

Due to the continuous recruiting until sample size is achieved, the study may last for six months from commencement of recruitment.

#### 1.10.1 Participant Duration

An individual participant will complete the study in about 14 days or 28 days depending on the response of the participant from screening at day -1 or 1 to follow-up on day 14 ±3 days. However, if the participant is responding, he can be treated until he recovers. Such a judgement will be made by the PI at the study site.

#### 1.10.2 Safety

* Indicate the therapeutic index (TI) of the herbal medicine here, if you know it.
* The EC/NRM will monitor the study. Furthermore, the DSMB will review safety data after every 50 study participants are entered into the trial and ad hoc reviews will be undertaken if there are other specific safety concerns. The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on the outcomes of their safety reviews.

###

### **1.11 Schedule of Assessments**

|  |  |  |
| --- | --- | --- |
|   | ***Screen*** | ***Baseline***  |
| **Day +/- Window** | **−1 or 1** | **1** | **Daily until hospital discharge** | **14** | **28** |
| **Time** |  |  |  |  |  |
| **Assessments/Procedures** |  |  |   |   |  |
| **ELIGIBILTY** |  |  |  |  |  |
| Informed consent | X |  |   |   |  |
| Demographics & Medical History | X |  |  |  |  |
| Review SARS-CoV-2 results | X |  |  |  |  |
|  |  |  |  |  |  |
| **STUDY INTERVENTION** |  |  |  |  |  |
| Randomization |  | X |  |  |  |
| Administration of XXX| control |   | Daily administration until discharge or Day 14 |  |  |
|  |  |  |  |  |
| **STUDY PROCEDURES** |  |  |   |  |  |
| Vital signs including SpO2 |  | X5 | Daily until discharge | X | X |
| Clinical data collection1  |  | X5 | Daily until discharge | X | X |
| Targeted medication review |  | X5 | Daily until discharge | X | X |
| Adverse event evaluation |  | X | Daily until discharge | X | X |
|  |  |  |  |  |  |
| **SAFETY LABORATORY** |  |  |  |  |  |
| Safety haematology, chemistry and liver tests2 | *X3* | X4,5 | Day 3, 5, 7, 14 |  |  |
| Pregnancy test for females of childbearing potential | *X3* |  |   |  |  |
|  |  |  |  |  |  |
| **RESEARCH LABORATORY**  |  |  |  |  |  |
| Blood for serum |  | X5 | Day 3, 5, 7, 14 | X | X |
| Blood for PCR SARS-CoV-2 |  | X5 | Day 3, 5, 7, 14 |  |  |
| Oropharyngeal swab |  | X5 | Day 3, 5, 7, 14 | X | X |

Notes:

1. *White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT/SGPT, AST/SGOT.*
2. *Laboratory tests performed in the 48 hours prior to enrolment will be accepted for determination of eligibility.*
3. *Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.*
4. *Baseline assessments should be performed prior to study drug administration.*
5. *In person visits are preferred but recognizing quarantine and other factors may limit the subject’s ability to return to the clinic. In this case, these visits may be conducted by phone.*

**2. INTRODUCTION**

**2.1 Repurposing of herbal medicines**

If a herbal medicine has already been registered by the NMRA for a particular disease, it can be repurposed for treatment of COVID-19 patients. If the innovator believes it can also be effective against COVID-19, the following steps should be followed:

If the dose for the treament of COVID-19 patients is the same as that used to register the product for trerament of another disease , then there is no need to do safety studies or dose-escalation studies (Phase 1). The only requirement is to carry out *in vitro* studies to determine if the herbal medicine kills the virus or stops the replication of the virus or prevents its attachment to the receptor sites or has immunomodulatory or antiinfalmmatory effect. Thereafter, the researcher can adapt this Standard Protocol. This document can be adapted for Clinical Trial Phases II and III. The key differences are the sample sizes and the number of study sites. In the case of phase II clinical trial, 200 study participants and one study site are adequate. Pilot or Phase IIA study is acceptable. But Pivot or Phase IIB is prefereed The main differences between phases IIA and IIB are that the latter is randomized, controlled and double-blind. However, in the case of phase III clinical study, it is randomized, dounle blind, placebo controlled of comparator-controlled, multicentre and sample size is 1000 and above.

However, if the dose of the repurposed herbal medicine to be used against COVID-19 is higher than the one indicated in the registered herbal medicine, then safety studies[[3]](#footnote-3) in animals must be conducted in addition to *in vitro* anti-viral studies[[4]](#footnote-4). If the results confirm safety at the higher dose level in animals, then safety study must be conducted in humans (Phase I).

**2.2 New herbal medicine against COVID-19**

If the herbal medicine is new and has not been registered by the NMRA, the innovator should first decide on the scope of product usage. The WHO has published Guidelines for the registration of traditional medicines in the WHO African Region[[5]](#footnote-5). The Guidelines included the minimum requirements for the registration of traditional medicines (eg safety, efficacy, quality, labelling and packaging). This protocol can be adapted for Category 3 traditional medicines. Under category 3 traditional medicines, safety, efficacy and quality data are based on research.

According to the WHO survey conducted in 2012,6 98 countries regarded technical guidance on research and evaluation of traditional and complementary medicine as their greatest challenge[[6]](#footnote-6). In addition to non-availability of effective pharmacological treatment for COVID-19, thie Standard Protocol has been developed to support countries to generate credible clinical data on herbal medicines since lack of such data is the most difficult challenge encountered by Member States *vis-à-vis* Traditional Medicines.

## 2.3 Study Rationale

The experts predict that Coronavirus 2019 will be with us for a long time7. Science knows that the virus transmits very easily and efficiently among humans. It may change to cyclical waves or remain with us as a low endemic disease[[7]](#footnote-7). **On 24th August 2020, the WHO released the following statement:9**

* **Nine CEPI-supported candidate vaccines are part of the COVAX initiative, with a further nine candidates under evaluation, and procurement conversations on-going with additional producers not currently receiving research and development (R&D) funding through COVAX – giving COVAX the largest and most diverse COVID-19 vaccine portfolio in the world**
* **80 potentially self-financing countries have submitted non-binding expressions of interest to the Gavi-coordinated COVAX Facility, joining 92 low- and middle-income economies that are eligible to be supported by the COVAX Advance Market Commitment (AMC)**
* **The goal of bringing the pandemic under control via equitable access to COVID-19 vaccines needs urgent, broad scale commitment and investment from countries**

.

The statement indicates good progress in vaccine development and preparations to make them available when the clinical trials are completed successfully.The developers use various approaches including protein subunit, non-replicating viral factor, live attenuated virus, inactivated virus, DNA, among others. It is hoped that one of these candidate vaccines will yield an effective vaccine. However, in reality at the moment we do not know if any of the candidate vaccines will confer effective protection against infection by SARS-COV2.  Furthermore, we do not know yet how long any such immunity will last. The current situation provides the urgent justification to explore other alternatives including traditional medicine, for new medical products that may alleviate symptoms, offer cure or confer immunity against SARS-COV2. Interestingly, some African medicinal plants have been reported to possess immune boosting and anti-inflammatory properties as well as anti-viral effects. The immense biodiversity in Africa and rich African indigenous medical knowledge (Traditional Medicine) provide unique opportunity for research and development of new medical products against COVID-19 either as prophylactics or treatments. However, such potential products must be evaluated for safety, efficacy and quality just like orthodox medicines.

**2.4 Purpose of Study**

Some countries in the WHO African Region have proposed traditional medicine-based therapies for the treatment of COVID-19 patients. This protocol is aimed at guiding countries on theclinical evaluation of such herbal medicines for the treatment of COVID-19 patients with mild to moderate symptons. The design is randomized double blind comparator- controlled clinical trial phase II or III of herbal medicine in the treatment of COVID-19 patients..

The site biostatistician will calculate the sample size... The formula for calculating the sample size is indicated in section 12 of this Standard Protocol. Additional 10% to the calculated sample size is recommended to account for withdrwals and or deaths. The selection of the study participants will be based on inclusion and exclusion criteria of the study. The study participants on the control arm will be treated with the national standard of care plus an inactive dommy product representing the herbal medicine. On the other hand, the Test Arm will receive the herbal medicine plus inactive dommy products representing the medicines given for standard care of treatment. The treatment (oral) with the herbal medicine is for fourteen (14) days. However, treatment may be extended to 28 days if the participant has not fully recovered by day 14 but improving clinically. Such a decision will be determined by the PI at the study site. Furthermore,, based on the continuous recruitment approach, the study may last for six months.

The purpose of this study is to compare the safety and efficacy profiles of the standardized herbal medicine against the standard of care with mild to moderate cases of COVID-19.

**2.5 Background information**

**2.5.1 Pathogenesis of COVID-19**

The pathogenesis of COVID-19 is crucial in its management. The management of COVID-19 is complicated by the large pool of asymptomatic populations who are carriers and can infect others unknowingly[[8]](#footnote-8). Studies which will facilitate the development of specific therapeutics to control the virus, minimize pulmonary injuries or optimize immune responses are urgently needed11.

SARS-CoV-2 is a member of the β-coronavirus family, and is partially related to the known SARS-CoV (~79% similarity) and MERS-CoV (~50% similarity) according to genomic sequencing. Both SARS-CoV, SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) as their main receptor site[[9]](#footnote-9). ACE2 is expressed in vascular endothelium, respiratory epithelium, alveolar monocytes, and macrophages. The main transmission route is through direct or indirect respiratory tract exposure. Patients with COVID-19 show clinical manifestations including fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia which are similar to the symptoms of SARS-CoV and MERS-CoV infections11.

The degeneration of symptoms is due to direct effect of the virus as well as immune-mediated injury induced by SARS-CoV-2. Furthermore, there is progressive increase of inflammatory response and a widespread hypercoagulation with prolonged prothrombin time and elevated levels of D-dimer and fibrinogen. A few patients would finally progress to overt disseminated intravascular coagulation (DIC). Tang et al13 reported that 71.4% of non-survivors and 0.6% of survivors of COVID-19 showed evidence of overt DIC. The high incidence of thromboembolic events suggests an important role of COVID-19-induced coagulopathy.

**2.5.2 Treatment**

There are various treatments given at different centres including steroids, antiviral and antibacterial agents as well as palliative management involving ventilators, etc. Usually, these medicines are given in combinations. Other treatments include glucocorticoids, high-dose intravenous immunoglobulin, anti-IL-6R antibody (tocilizumab, etc.), convalescent plasma therapy and other immunomodulators. A recent publication on 12 autopsies of those who died from COVID-19 indicated that the main cause of death for most of them was coagulopathy13.. Consequently, anticoagulants and anti-inflammatory agents may be relevant for the treatment of some COVID-19 patients. Alexander and his coworkers14 identified three stages of infection at which the coronavirus could be targeted include keeping the virus from entering the cells, preventing it from replicating inside the cells, and minimizing virus-induced damage to the organs.

Although management of severe and critical COVID-19 patients is crucial to reduce the mortality of the pandemic, the realistic measures include prevention, monitoring, testing, effective contact tracing mechanism and timely intervention.

**2.5.3 Pre-clinical data on safety & efficacy**

The preclinical data should be based on *in vitro* studies regarding the antiviral effect of the product (either death, anti-replication or competition at angiotensin converting enzyme receptor sites). Such experiments are mandatory if the product targets specific treatment of COVID-19 patients. However, if the product is intended to be used for preventive purposes, then effects on markers of the immune responses will be adequate. Examples of such studies include macrophage activation assay, monocyte cytokine release, anti-inflammatory assay, etc. *In vitro* safety evaluation include cytotoxicity, hepatotoxicity and genotoxicity. *In vivo* studies involving animals are mandatory to evaluate safety of the potential herbal medicine. However, this protocol is specifically for safety and efficacy evaluation of herbal medicines for the trearment of COIVID-19 patients. If the product targets treatment of COVID-19 patients, then acute and sub-acute (14 days) toxicity evaluation may be adequate. However if the product is intended for prophylaxis, then sub-chronic toxicity evaluation (90 days) must also be undertaken. At the end of each evaluation, histopathology of major organs (eg heart, kidney, brain, lungs, etc) should be carried out. However, if the product is intended to be used for both curative and prophylactic purposes, all the safety studies indicated above should be undertaken. The methodologies for undertaking these tests are indicated in the WHO guidelines for non-clinical studies3.

This Standard Protocol is designed for evaluation of WHO Trdaitional Medicine Category 3. Consequently, bio-guided fractionation leading to purification, isolation and structural characterisation of the bioactive compounds is highly recommended. In addition, such studies will enhance patenting at the World Intellectual Property Organization (WIPO), publication in international peer-reviewed journals and licensing to reputable international pharmaceutical companies. Furthermore, pharmacokinetic studies can be executed in laboratory animals using the bioactive compounds which will guide in dosage schedule.

The summary of the pre-clinical studies should be included here while the detailed data should be in the Investigators’ Brochure (IB).

**Therapeutic Index**

Therapeutic Index (TI) is the measurement of drug safety and refers to between toxic and therapeutic doses. The formula for calculating the Therapeutic Index is: TI=LD50/TD50

LD50 = Lethal dose that kills 50% of animals.

TD50 = Effective dose in 50% of animals.

Note that LD50 is used when dealing with laboratory animals while TD50. is used when dealing with humans.

The higher the TI of a new medical product the safer it will be in clinical use.

Figure 2 below shows the relationship between therapeutic effect and toxic effect[[10]](#footnote-10).

**Figure 2:** Drug Safety-Therapeutic Index.

|  |
| --- |
|  |
|   |

<https://step1.medbullets.com/pharmacology/107009/therapeutic-index> visited on 17th July 2020.

**2.6 Risk/Benefit Assessment.**

The therapeutic index will be a useful guide in the risk/benefit assessment. Biochemical and haematological evaluations of the extracts in rats during the safety assessment studies will also indicate their safety profiles regarding those parameters. Include summary of the safety assessment here while the detailed data should be included in the IB. If the herbal medicine has been used for more than 25 years with evidence of safety, the available ethnomedical data should be included here

# **OBJECTIVES AND ENDPOINTS**

The overall objective of the study is to evaluate the clinical efficacy and safety of herbal medicine in comparison to the control arm on national standard of care in the management of adult patients with mild to moderate cases of COVID-19.

| **OBJECTIVES** | **ENDPOINTS (OUTCOME MEASURES)** |
| --- | --- |
| **Primary** |  |
| 1. The overall objective of the study is to evaluate the clinical efficacy of herbal medicine relative to the control arm in adult patients hospitalized with COVID-19.
* The primary endpoint is cure or death.
* Subject clinical status (on a 7-point ordinal scale) at day 7 is the default primary endpoint.

Evaluate the virologic efficacy of herbal medicine as compared to the control arm as assessed by:Herbal medicine as compared to the control arm as assessed by:* Percent of subjects with SARS-CoV-2 detectable in OP sample at day 3, 5, 7, 14, and 28.
* Quantitative SARS-CoV-2 virus in OP sample at day 3, 5, 7, 14 and 28.
* Development of resistance of SARS-CoV-2 in OP sample at day 3, 5, 7, 14, and 28.
* Quantitative SARS-CoV-2 virus in blood at day 3, 5, 7 and 14.
 | 1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Cure
5. Death.
* Qualitative and quantitative PCR for SARS-CoV-2 in OP swab on Days 1; 3, 5, 7, 14 (while hospitalized); and Day 28 or until the patient is negative.
* Qualitative and quantitative PCR for SARS-CoV-2 in blood on Days 1; 3, 5, 7, 14 (while hospitalized).
 |
| **Secondary** |  |
| 1. Evaluate the clinical efficacy of herbal medicine as compared to the control arm as assessed by:**Clinical Severity*** Ordinal scale:
	+ Time to an improvement of one category from admission using an ordinal scale.
	+ Subject clinical status using ordinal scale at days 3, 5, 7, 14 and 28.
	+ Mean change in the ordinal scale from baseline to days 3, 5, 7, 14 and 28 from baseline.
 | * Ordinal outcome assessed daily while hospitalized and on day 7 or 14.
 |
| * National Early Warning Score (NEWS):
	+ The time to discharge or to a NEWS of ≤ 2 and maintained for 24 hours, whichever occurs first.
	+ Change from baseline to days 3, 5, 7, 14 and 28 in NEWS
 | * NEWS assessed daily while hospitalized and on day 7 or 14
 |
| * **Hospitalization**
	+ Duration of hospitalization (days).
 | * Duration of hospitalization
 |
| * **Mortality**
	+ 7-day mortality
 | * Date and cause of death (if applicable
 |
| 1. Evaluate the safety of the intervention through 28 days of follow-up as compared to the control arm as assessed by:
* Cumulative incidence of serious adverse events (SAEs) through 28 days of follow-up.
* Cumulative incidence of Grade 3 and 4 AEs.
* Discontinuation treatment with herbal medicine (for any reason)
* Changes in white cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST over time.
 | * SAEs
* Severe adverse events
* White cell count, haemoglobin, platelets, creatinine, glucose, total bilirubin, ALT, and AST on days 1; 3, 5, 7, 14 (while hospitalized); and Day 28 (if able to return to clinic or still hospitalized).
 |

**4. QUALITY ASSURANCE SYSTEMS**

A quality assurance system is essential to ensure that herbal processing practice is consistently executed and controlled. The system for verification of compliance may differ from country to country. In general, compliance with quality assurance measures should be verified through regular internal oversight personnel (quality assurance manager) and external auditing visits to processing facilities by expert representatives of buyers and other stakeholders, and through inspection by NMRA. No processed herbal medicine should be released until its quality complies with or conforms to standard specifications. The WHO has published the Good herbal processing practices (GHPP) which can be adaptted appropriately[[11]](#footnote-11).

In view of the fact that the chemical constituents of plants are subject to variation depending on the soil, weather, season, age of the plant, time of harvesting, etc, it is mandatory to establish a chemical marker or fingerprint using chromatographic techniques. Each batch of plant raw materials collected should be subjected to the fingerprint so as to guarantee consistent biological response of the final product. Furthermore, the plant samples should be tested for microbiological, heavy metal and pesticide contaminations using appropriate spectroscopic techniques. The WHO Quality Control Methods for herbal materials is a good reference for quality assessment of the plant materials[[12]](#footnote-12) .

In view of the fact that the chemical constituents of medicinal plants are subject to variation depending on the soil, weather, season, age of the plant, time of harvesting, etc., WHO guidelines on WHO Good Agriculture and Collection Practices[[13]](#footnote-13) (GACP) should be adhered to. It is mandatory to establish a chemical marker of fingerprint using chromatographic techniques. Each batch of medicinal plant raw materials collected should be subjected to the fingerprint so as to guarantee consistent biological response of the final product. Furthermore, the medicinal plant samples should be tested for microbiological, heavy metal and pesticide residue contaminations according to WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (GAQ)[[14]](#footnote-14), Quality control methods for herbal materials (QCM)[[15]](#footnote-15) and using appropriate spectroscopic techniques. The GHPP guidelines intended to supplement technical guidance on processing in the post-harvest stages and integrally linked to GACP and Good Manufacturing Practices (GMP)[[16]](#footnote-16) , provide technical guidance on GHPP in the: processing of herbs into herbal materials; processing of herbal materials into herbal preparations; and processing of herbal materials or herbal preparations into herbal dosage forms. It is also relevant to identify and quantify any essential oils in the medicinal plant samples using Gas Chromatography.

Quality assurance systems are particularly relevant while conducting clinical trial with traditional herbal medicines because there are various factors that can impact on the quality of the product and consequently on the quality of the data and health of the trial subjects. Examples of such factors include method and timing of plant collection, location of plants, harvesting and post-harvesting processing, product preparation procedure, storage, natural additives, preservatives and packaging. The WHO Good Storage and Distribution Practices (GSDP) is highly recommended for adaptation appropriately. Thus, a planned method for standardising the raw materials, finished products and the processes involved right from collection of the raw materials to the manufacturing of the product should be articulated and adhered to through appropriate standard operating procedures (SOPs).

A realistic monitoring system should also be developed and implemented. Study specific SOPs have been developed to ensure quality management and will be used to train study personnel and kept on file with documentation of training. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, WHO Good Clinical Practice (GCP)15, and the applicable regulatory Investigators will provide direct access to source data/documents, and reports for the purpose of monitoring and auditing by the monitoring sponsors, and inspection by local and regulatory authorities. **Study** staff will be responsible for the quality control implementation during both data collections into source documents and CRFs and during transcription of data into the electronic CRF system through secure data entry and data quality checks within the database. All missing data or anomalies will be discussed with the study clinicians and nurses for clarification/ resolution. The monitoring of QAS should be undertaken by NMRA who sends a qualified person to the study site. An independent monitoring will be provided by the Regional Expert Advisory Committee on Traditional Medicine (REAC).**5. ROADMAP FOR TRADITIONSAL MEDICINE RESEARCH AND DEVELOPMENT**

Figure 3 below depicts the key activities regarding research and development of standardized herbal medicines. It should be noted that the roadmap starts with the THPs because they are the custodians of indigenous medical knowledge (IMK). The choice regarding the selection of medicinal plants for the study is based on ethnomedical evidence from the THPs. The Memorandum of Understanding (MoU) is to provide a legal platform for engaging the THPs in the R & D processes and also beneficiary (both financial and in kind) if the product is marketed. The collection and processing of medicinal plant samples, QAS should be undertaken using the appropriate WHO technical documents (i.e. GAQ, GACP, GHPP and QCM). The first quality control activity is to assess the quality of the plant samples with reference to contaminants and residues using the WHO GAQ technical document. It is noteworthy that after the bio-guided fractionation leading to the bioactive fractions, the rest activities are virtually the same as when developing a medicinal product from a synthetic compound.

**Figure 3:** Road map for traditional herbal medicine research and development



**6. STUDY DESIGN**

## 6.1 Overall Design

This study is a randomized, double-blind, controlled phase III trial to evaluate the safety and efficacy of the herbal medicine in adult participants diagnosed with mild to moderate symptons of COVID-19 infection. The study site will be determined after EC/NMRA approval following a pre-trial inspection. The study will be a 2-arm comparison between herbal medicine and an inactive dommy product ( plus national standard of care treatment). Since it is a double-blind study, both arms will receive the same number of medicines only that the Control Arm will be given the standard care of treatment (plus inactive dommy product representiing the herbal medicine) while the Test Arm will use the herbal medicine plus inactive dommy products (representing the orthodox medicines given for stanrdard of care). An independent DSMB will actively monitor interim data to make recommendations about early study closure or changes to study arms when and if necessary.

Randomization will be stratified by:

* Site
	+ Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

Participants will be assessed daily for fourteen (14) days or 28 days depending on the responses of the study participants. The PIs at the study sites will make such decisions. . Then there will be follow-up visits on 28 days for cured participants and thereafter monthly for six (6) months. All participants will undergo a series of efficacy, safety, and laboratory assessments. Oropharyngeal (OP) swabs will be obtained on days 1, 3, 5, 7 and 14 and day 28. The schedule will vary depending on the pharmacokinetic profile of the herbal medicine (if available) and or time needed for total viral clearance.

The primary outcome, assessed on a 7-point ordinal scale at day 7 or 14 will be complete clearance of viral load or significant progressive reduction of the viral load in OP swabs on days 28 and monthly until the patient is negative. The secondary outcomes will be time to improvement, duration of stay at hospital, (if applicable fior some participants), development of adverse or severe adverse events, changes (if any) on heart, liver, kidney and lung functions and complete blood count.

## 6.2 Scientific Rationale for Study Design

Presently, there is no specific antiviral therapy for the treatment of coronavirus infection. Recent studies have indicated some benefits in patients with severe cases given remdesivir injection (an antiviral agent)1. Similarly, dexamethasone demonstrated significant benefits in severe cases of COVID-19 infection2. Since both redensivir are only useful in severe cases of COVID-19 infection, they cannot be used as comparators in this study because only mild to moderate cases are qualified for selection.

# Summary of the results regarding the safety and efficacy profiles in two rodent species provide the scientific justification for the clinical trials phase III of the herbal medicine in the management of COVID-19 patients.. Alternatively, credible ethnomedical evidence regarding the safe use of the herbal medicine is accepted as justification for the clinical evaluation of suich herbal medicine, especially in a pandemic.

**6.3. Study Site Research Team**

The research Team should comprise of the Principal Investigator (PI) who must be a medical doctor with relevant speciality (eg infectious diseases, internal medicine, etc) at the level of professor or consultant with clinical trial research experience. The PI should be assisted by another medical doctor at the level of a consultant. Other members of the Research Team should include a pharmacist, nurses, laboratory technologists, pharmacognist, biostatistician and epidemiologist. The composition will vary taking cognizance of applicable national regulations and IRB/EC requirements.

**6.4 Data Safety and Monitoring Board (DSMB)**

The members of the DSMB serve in individual capacities and provide their expertises and recommendations to the sponsors. The DSMB Charter for this study has been developed which includes the terms of reference and objectives.

## 6.5 Justification for Dose

The dose is based on a combination of factors including the dose used by the traditional health prcatitioner (THP), the preclinical data on efficacy, dose escalation studies/pharmacokinetics (where available)..

# **7. STUDY POPULATION**

The sample size will be calculated by the biostatistician at the trial site. Men and non-pregnant female adults (≥18 years of age) with mild to moderate cases of COVID-19 who meet all the selection criteria will be enrolled for the study. However, the exact number of sample size will be calculated using the formula provided in this protocol by each country based on prevailing confirmed cases of COVID-19. The estimated time from screening (day -1 or day1) to end of study for an individual participant is approximately 14 days or 28 days depending on the responses of the study participants. The recruitment mechanism will be designed at each site taken cognizance of cultural sensitivities and applicable regulations. However, such recruitment process and materials must be approved by the EC//NMRA prior to commencement of the study.

### **7.1 Inclusion Criteria**

* Study participant (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
* Understands and agrees to comply with planned study procedures.
* Agrees to the collection of OP swabs and venous blood per protocol.
* Male or non-pregnant female adult ≥18 years of age at time of enrolment.
* Laboratory-confirmed SARS-CoV-2 infection as determined by PCR at a Government approved lab. from throat/nasopharyngeal swab.
* Illness of any duration, and at least one of the following:
* Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or
* Creatinine ≤ 110 umol/L, creatinine clearance rate (EGFR) ≥ 60 ml / min / 1.73m2, AST and ALT ≤ 5 × ULN, TBIL ≤ 2 × ULN;
* A Normal ECG baseline result, which is maintained throughout the study.

 **7.2 Exclusion criteria**

Study participants with the following conditions will be excluded from the study:

* ALT/AST > 2 times the upper limit of normal.
* Stage 2 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
* Pregnancy or breast feeding.
* Anticipated transfer to another hospital which is not a study site within 72 hours.
* Allergy to any study medication
* Shortness of breath in resting position
* Known prolonged QT syndrome
* Use of concomitant medications that prolong the QT/QTc interval
* Participant with other viral pneumonia
* History of allergic reactions to any investigational medical product ingredient

Study participants who in the opinion of the investigators after assessing all relevant parameters are unsuitable for the study.

### **7.3 Lifestyle Considerations**

During this study, study participants are asked to avoid alcohol and tobacco.

### **7.4 Screen Failures**

After the screening evaluations have been completed, the investigator or designee is to review the inclusion/exclusion criteria and determine the participant’s eligibility for the study. Participants who are found to be ineligible will be told the reason for ineligibility. Individuals who do not meet the criteria for participation in this study (screen failure) because of an abnormal laboratory finding may be rescreened once. Participants who are not eligible for this study will be treated in accordance with the national standard of care.

### **Strategies for Recruitment and Retention.**

#### 7.5.1 Recruitment

Methods of recruitment can be articulated based on cultural sensitivities and applicable national regulations provided the EC/NMRA approves them. Participants that are PCR confirmed to have SARS-CoV-2 will be assessed for eligibility.

Screening will begin with a brief discussion with the research team. Some will be excluded based on demographic data and medical history, (eg < 18 years of age, renal failure, etc). Information about the study will be presented to potential subjects (or legally authorized representative) and questions will be asked to determine potential eligibility. Screening procedures can begin only after informed consent is obtained. The details regarding recruitment are contained in the Standard Operating Procedures (SOPs) for this study.

#### 7.5.2 Retention

Study participants will be adequately briefed on the importance of hospital visits upon their discharge while an active follow up programme will be implemented.

#### 7.5.3 Compensation Plan for Study Participants.

Compensation, if any, will be determined locally and in accordance with local IRB requirements, and subject to local EC//NMRA approvals and national regulations.

#### 7.5.4 Costs

There is no cost to participants for the research tests, procedures/evaluations and herbal medicine while taking part in this trial. Procedures and treatment for clinical care including costs associated with hospital stay will be the responsibility of the sponsor.

# **8. STUDY PRODUCT**

## 8.1 Study Product and Administration

### **8.1.1 Study Product Description**

Since this is a double-blind study, the supplied matching inactive dommy products must be identical in physical appearance and taste to the herbal medicine and contains the same inactive ingredients and must comply with NMRA requirements.

***Dommy Products***

The dommy products will contain the same inactive ingredients as the herbal medicine. The storage condition (25 ± 5 °C) will be the same as for the herbal medicine.. The two products will be shipped directly to each study site. At each study site, quality assessment including stability test will be carried out. At sime study sites, the inactive dommy products can be produced if relevant facilities and expertise are available

#### Dosing and Administration

Study participants will be randomized to receive either the herbal medicine plus the inactive dommy products (representing the orthodox medicines given to the Control Arm on standard of care treatment) or standard of care treatment plus one inactive dommy product (representing the herbal medicine given to th participants on the Test Aarm)

A protocol-specific SOPs hve been developed which will contain detailed information on the preparation, labelling, storage, and administration of the herbal medicine and dommy products.

***Dose schedule and route of administration***

Indicate here the dose schedule and route of administration based the ethnomedical use or dose escalation studies .

***Treatment duration***

The drug administration is for 14 days or 28 days depending on the responses of the study participants. However, the treatment can be continued for 28 days if the study participant has not fully recovered but improving significantly. Such decision is the responsibility of the PIs at the study sites. But since recruitment is on a continuous basis, the study duration is based on when the sample size is achieved which may be up to six months.

### **8.1.2 Preparation/Handling/Storage/Accountability**

#### Acquisition and Accountability

The herbal medicine will be shipped to the study site directly from the manufacrurer in a secured manner in accordance with NMRA requirements. Alterenativl;y, the herbal medicine and the inactive dommy products can be manufactured at the study site provided relevant facilities and personnel with expertise are avaialble.

#### Accountability

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site’s research pharmacist the responsibility for study product accountability.

The participating site’s research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the herbal medicine. Time of study drug administration to the subject will be recorded on the appropriate case report form (CRF). If a patient vomits during treatment with the herbal medicine, he/she will be excluded from the study and given the national standard of care.

The herbal medicine, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The sponsor’s monitoring staff will verify the participating site’s study product accountability records and dispensing logs per the site monitoring plan. Refer to the protocol-specific SOP for details on storrage...

#### Destruction

After the study treatment period has ended or as appropriate over the course of the study after study product accountability has been performed, disposition of unused and used herbal medicine and inactive dommy products should be undertaken as follows:

Unused and Used herbal medicine and inactive dommy products:

* Should be returned to the sponsor or destroyed on-site following applicable site procedures or by the site’s selected destruction vendor. Following the site’s procedure for the destruction of hazardous material or SOP when destroying used and unused items.
* A certificate of destruction should be provided to the sponsor and retained in the Pharmacy Binder once completed.

### **8.1.3 Formulation, Appearance, Packaging, and Labelling according to NMRA requirements.**

***Inactive dommy product to match***

The supplied matching inactive dommy products must be identical in physical appearance to the herbal medicine ( in case of the Control Arm) formulation and contains the same inactive ingredients. However the inactive dommy products representing the orthodox medicines gioven for the standrd of care treatment must have the same physical characteriustivs as the orthodox medicines (Test Arm). The dommy products will be labelled according to manufacturer’s specifications and must include the statement “Caution: New Drug Limited by Regulatory Authority to Investigational Use.”

### **8.1.4 Product Storage and Stability**

### Indicate storage conditions of the herbal medicine here.

### **8.1.5 Preparation**

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

**9. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING**

The study will randomize participants 1:1 to medical products or inactive dommy products Randomization will be stratified by:

* Site
* Severity of illness at enrolment:
	+ Mild-moderate disease: SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

The randomization procedure has been described in the SOP including procedures for blinding.

## 9.1 study intervention compliance

Each dose of herbal medicine and the inactive dommy products will be administered by a member of the clinical research team that is qualified and licensed to administer the study product. Administration and date and time will be entered into the CRF.

# **10. STUDY INTERVENTION DISCONTINUATION AND STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL**

## 10.1 Halting Criteria and Discontinuation of Study Intervention

### **10.1.1 Individual Halting of Treatment**

The treatment with the herbal medicine must be stopped immediately there is a drug-related hypersensitivity (Grade 2 or higher). Such study participants will not continue on the herbal medicine If a study participant vomits during treatment with the herbal medicine, he/she will be excluded from the study and given the national standard of care.

### **10.1.2 Study Halting for Safety**

Close monitoring by the study research team is mandatory. Furthermore, frequent DSMB reviews for safety should be fostered. Treatment should be stopped if a study participant is found to be pregnant after randomization

### **10.1.3 Withdrawal from Randomized Treatment or from the Study**

Participants are free to withdraw from participation in the study at any time upon request, without any consequence. Participants should be listed as having withdrawn consent only when they no longer wish to participate in the study and no longer authorize the Investigators to make efforts to continue to obtain their outcome data. Every effort should be made to encourage participants to remain in the study for the duration of their planned outcome assessments. Participants should be educated on the continued scientific importance of their data, even if they discontinue.. In the case of a participant becoming lost to follow-up, attempts to contact him or her should be made and documented in the participant’s medical records.

### **Withdrawal policy**

### A participant in this clinical study may on his own volition discontinue herbal medicine treatment. Those who discontinue study drug early should remain in the study for further acquisition of endpoint measurements. The reason for participant’s discontinuation of study drug should be documented in the case report form. However, whenever possible the study participant should be followed for safety evaluations as per this protocol: Participants who withdraw from this study or are lost to follow-up after signing the informed consent form (ICF) and administration of the herbal medicine will not be replaced.

Any participant is free to discontinue the trial at any time during the study. On the other hand, the PI may withdraw a participant from the study due to serious adverse reactions (eg anaphylaxis and allergic symptoms of dyspnea or wheezing, itching or erythema). Furthermore, a participant may be withdrawn if he/she fails to respond to the treatment with the herbal medicine and his/her condition is deteriorating.

If a participant has Grade 1 or 2 toxicity only but desires further therapy, the drug may be resumed after 72 hours break at 50% of the offending dose. If this is tolerated after 72 hours, the dose may be increased to 75% of the offending dose with close monitoring. The PI should consider probable development of resistance with such retreatment option.

***Reasons for Discontinuation of Treatment***

* Participant withdraws consent or requests discontinuation from the study for any reason
* Participant fails to comply with protocol requirements or study-related procedures
* Death of the participant
* Termination of the study
* Lost to follow-up.
* Increase in hemolysis during the study period as indicated by a rise in free plasma hemoglobin, LDH, bilirubin and a fall in hemoglobin and hematocrit.
* Grade 3 or 4 toxicity rating
* Participant’s voluntary discontinuation with the study
* Major Protocol deviation
* Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
* Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the participant.

All severe reactions must be reported within 24 hours.

**10.1.5 Treatment of adverse effects**

It should be emphasized that the PI has the professional responsibility with regards to the management of adverse effects. It is recommended that appropriate interventions should take cognizance of the national standard treatment guidelines and associated complications. More details are contained in the SOPs.

### **10.1.6 Lost to Follow-Up**

A participant will be considered lost to follow-up if he or she fails to appear for a follow-up assessment and cannot be contacted with good efforts. These efforts will be documented in the participant’s record.

# **11. STUDY ASSESSMENTS AND PROCEDURES**

## Screening and Efficacy Assessments

### **Screening Procedures**

After the informed consent is administered and a day before dosing, the following tests shall be undertaken for both the test and control arms of the study participants. to determine eligibility requirements as specified in the inclusion and exclusion criteria:

* Confirm the positive SARS-CoV-2 test result.
* Medical history, including:
* Day of onset of COVID-19 symptoms
* History of chronic medical conditions related to inclusion and exclusion criteria
* Medication allergies
* Review medications and therapies for this current illness and record on the appropriate CRF.
* Counsel study participants to use adequate birth control methods required during the trial to avoid pregnancy.
* Review recent radiographic imaging (x-ray or CT scan)
* Targeted physical exam focused on lung auscultation
* Obtain blood for screening laboratory evaluations if not done in the preceding 48 hours:
	+ - Cr (and calculate creatinine clearance)
		- Urine or serum pregnancy test (in women of childbearing potential)
* Weight, height
* Vital signs
* ECG, chest x-ray
* Full blood count, WBC, differential, HCT, Hgb, platelets
* Prothrombin time, partial thromboplastin time
* G6PD screen
* Blood chemistry (Na, K, Cl, CO2, BUN, Creatinine, Albumin, Alkaline phosphatase, LDH, ALT, AST, bilirubin total and direct, hepatitis panel, glucose, cholesterol, triglericides.
* Cardiac panel: creatinine kinase, MB, Myoglobin and troponin levels in the cardiac muscle, creatinine clearance rate eGFR rate, amylase.
* Virology index: CD4, CD8 counts, Nasopharyngeal swab sampling for Covid-19 viral load.
* Urinalysis: PH, Gram stain, glucose, colour, cells, protein,
* On day 1 immediately prior to dosing, repeat measurement of vital signs.
* Determine HIV status.
* If the participant is female, confirm that she is not pregnant through pregnancy test and check on which contraceptive measure she is using.

Clinical screening laboratory evaluations will be performed locally at the site laboratory. The overall eligibility of a potential participant in the study will be assessed once all screening values are available. The screening process can be suspended prior to complete assessment at any time if exclusions are identified by the study team. Study participants who qualify will be immediately randomized.

**11.1.2 Efficacy Assessments**

For all baseline assessments and follow-up visits, refer to for procedures indicated in Investigator’s Brochure.

#### Ordinal Scale

The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on day 3, day 2 score is obtained and recorded as day 2. The scale is as follows:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities;
3. Hospitalized, not requiring supplemental oxygen;
4. Death.

#### NEW Score

The NEW score has demonstrated an ability to discriminate study participants at risk of poor outcomes. This score is based on 7 clinical parameters. The NEW Score is being used as an efficacy measure.

This should be evaluated at the first assessment of a given study day. These parameters can be obtained from the hospital chart using the last measurement prior to the time of assessment. This is recorded for the day obtained. i.e. on Day 3, Day 3 score is obtained and recorded as Day 3.

**Table 1:** **NEW Score**

*Level of consciousness = alert (A), and arousable only to voice (V) or pain (P), and unresponsive (U).*

**The research team at the trial site may choose to use other measures to score the study participants. The above is just an example.**

**11.1.3 Viral shedding**

OP swabs will be collected on days 1; 3, 5, 7 and 14 as well as 28

## 11.2 Safety and Other Assessments

Study procedures are specified in the SOA. The PI is responsible for all trial-related medical decisions.

* Physical examination: A symptom-directed (targeted) physical examination will be performed to evaluate for any possible adverse event. No physical exam is needed for routine visits.
* Clinical laboratory evaluations:
	+ Fasting is not required before collection of laboratory samples.
	+ Blood will be collected at the time points indicated in the SOA. Clinical laboratory parameters include WBC, Hgb, PLT, Cr, glucose, total bilirubin, AST, ALT.
	+ This testing will be performed at each clinical trial site in real time.

**Table 2:** Venepuncture Volumes

|  |  |  |
| --- | --- | --- |
|   | ***Screen*** | ***Baseline***  |
| **Day +/- Window** | **−1 to 1** | **1** | **2** | **3** | **5+1** | **7 ± 1** | **14 ± 2** | **28 ± 3** |
| Safety haematology, chemistry and liver tests21 |   | X6mL |  |  X6mL | X6mL | X6mL |   |  |
| Blood for Serum  |   | X24mL |  | X24mL | X24mL | X24mL |  X24mL | X24mL |
| Plasma (includes PCR) |  | X8mL |  | X8mL | X8mL | X8mL | X | X |
| Total volume |  | 38ml |  | 38mL | 38ml | 38ml | 24mL | 24mL |
| Total all study days |  |  |  |  |  |  |  | 238 mL |

### **11.2.1 Procedures to be Followed in the Event of Abnormal** **Laboratory Test Values or Abnormal Clinical Findings**

If a physiological parameter, e.g., vital signs, or laboratory value is outside of the protocol-specified range, then the measurement may be repeated once if, in the judgment of the investigator, the abnormality is the result of an acute, short-term, rapidly reversible condition or was an error.

A physiological parameter may also be repeated if there is a technical problem with the measurement caused by malfunctioning, or an inappropriate measuring device (i.e., inappropriate-sized BP cuff).

## 11.3 Adverse Events and Serious Adverse Events

### **11.3.1 Definition of Adverse Event (AE)**

AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

Any medical condition that is present at the time that the study participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE. All Grade 3 and 4 AEs will be captured as AEs in this trial.

### **Definition of Serious Adverse Event (SAE)**

An SAE is defined as “An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

* Death,
* a life-threatening AE,
* inpatient hospitalization or prolongation of existing hospitalization,
* a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
* or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, when, based upon appropriate medical judgment, they may worsen the case of the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.”

“Life-threatening” refers to an AE that at occurrence represents an immediate risk of death to a study participant. An event that may cause death if it occurs in a more severe form is not considered life-threatening. Similarly, a hospital admission for an elective procedure is not considered a SAE. All SAEs, as with any AE, will be assessed for severity and relationship to study intervention and recorded in the appropriate SAE CRF. All SAEs will be followed through resolution or stabilization by the PI. All SAEs will be reviewed and evaluated and will be sent to the DSMB (for periodic reviews), and the IRB/IEC.

### **Suspected Unexpected Serious Adverse Reactions (SUSAR)**

A SUSAR is any SAE where a causal relationship with the herbal medicine is at least reasonably possible but is not listed in the Investigator’s Brochure (IB), Package Insert, and/or Summary of Product Characteristics.

### **Classification of an Adverse Event**

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians and nurses.

#### Severity of Adverse Events

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

* Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject’s usual activities of daily living.
* Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
* Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
* Severe (Grade 4): Events that are potentially life threatening.

AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop Duration of each reported AE will be recorded on the appropriate CRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

#### Relationship to Study Intervention

For each reported adverse reaction, the PI or designee must assess the relationship of the event to herbal medicine using the following guidelines:

* Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
* Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

### **Time Period and Frequency for Event Assessment and Follow-Up**

For this study, all Grade 3 and 4 AEs and all SAEs occurring from the time the informed consent is signed through the day 14 (end of study as in-patients ) visit will be documented, recorded, and reported.

#### Investigators Reporting of AEs

Information on all AEs should be recorded on the appropriate CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than the individual laboratory abnormality. Each AE will also be described in terms of duration (start and stop date), severity, association with the study product, action(s) taken, and outcome.

### **Serious Adverse Event Reporting**

The reporting will be done according to NMRA requirements.

#### Investigators Reporting of SAEs

Any AE that meets a protocol-defined criterion as a SAE must be submitted immediately (within 24 hours of site awareness) on an SAE form to the designated Pharmacovigilance Group, at the following address:

Insert name and contact details of pharmacovigilance focal point

Other supporting documentation of the event may be requested by the designated Pharmacovigilance Group and should be provided as soon as possible. The designated Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE, the site PI or appropriate sub-investigator will report the event to the designated Pharmacovigilance Group. Following notification from the site PI or appropriate sub-investigator, report will be made to the NMRA while all participating site PIs and the DSMB are notified as soon as possible. Any unexpected fatal or life-threatening suspected adverse reaction will be reported to the NMRA as soon as possible. If the event is not fatal or life-threatening, the safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting. Relevant follow up information to a safety report will be submitted as soon as the information is available. Upon request from regulatory authority, the sponsor will submit any additional data or information that the agency deems necessary, as soon as possible, but not later than 15 calendar days after receiving the request.

### **Reporting Events to Study Participants**

Participants will be informed of any severe AEs or SAEs that occur as part of their participation in this trial.

### **Reporting of Pregnancy**

Pregnancy is not an AE. However, any pregnancy that occurs during study, participation should be reported to the sponsor on the appropriate CRF. All femalle participants are to be tested for pregnancy during screening.

11.4 Unanticipated Problems

### **Definition of Unanticipated Problems (UP)**

An Unanticipated Problem is any event, incident, experience, or outcome that meets the following criteria:

* Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
* Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
* Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### **Unanticipated Problem Reporting**

To satisfy the requirement for prompt reporting, unanticipated problems (UP) will be reported using the following timeline:

* UPs that are SAEs will be reported to the IRB and the DSMB and the sponsor within 24 hours of the investigator becoming aware of the event per the above describe SAE reporting process.

### **Reporting Unanticipated Problems to Study Participants**

The study participants will be informed of any UPs that occur as part of their participation in this trial.

# **12. STATISTICAL CONSIDERATIONS**

This will be done by the biostatistician at the study site. But the following calculation was based on the confirmed cases in Africa on 9th July 2020 as an example. The whole of this section will be determined by the biostatistiician at the study site.

## Statistical Analyses

##

## Sample size calculation and Statistics

This is just an example to guide the biostitstician.

SAMPLE SIZE:

In A’Hernapproach ,

Assumingα = 0.05, β = 0.20,

power = 0.80, P0( standard treatment or Placebo)= 10%,

P1 (new treatment) = 20% ,

d = difference between P1 and P0

$$N=\frac{Z 2 x P0(1-P0)}{d2}$$

The Sample size is 96 and with 10% dropout , it will be 105.6 = 106, which will be divided into two groups. Each group will have a sample size of 53. The sample size per study site is 106. However, for a Phase III clinical trial, 1000 study participants are needed. Thus, 10 study sites within and across countries will be tragetted to comply with this Standard Protocol

**Data Analysis**

SPSS VERSION 26 (IBM, ARMONK, NEW YORK, US) will be used.

* **Description of statistics**

The primary indicators collected in this study are described with statistical method. Quantitative indicators are described by means of mean, standard deviation, median, quartile, maximum, minimum and the like; qualitative indicators are described by frequency, percentage and the relationship.

Unless otherwise specified, the statistical significance level is 0.05 by two-sided test (one-sided 0.025) and Fisher exact test will be used to analyse the qualitative indicators while Means of quantitative data will be compared using ANOVA.

### **12.2 General Approach**

This is a double-blind placebo controlled randomized trial testing a superiority hypothesis with a two-sided type error rate of 0.05. Secondary hypotheses have been ordered according to relative importance. These will be described according to the appropriate summary statistics (e.g., proportions for categorical data, means with 95% confidence intervals for continuous data, median for time-to-event data).

A statistical analysis plan (SAP) will be developed and filed with the study sponsor prior to unblinding of study and database lock.

### **12.3 Analysis of the Primary Efficacy Endpoint**

The ordinal scale will be used to estimate a proportional odds model. The research team at the trial site may adopt another way to assess the efficacy provided it is approved by both the EC and NMRA. The primary hypothesis test will be based on a test of whether the common odds ratio for treatment is equal to one. As noted earlier, the hypothesis test is, for large sample sizes, nearly the same as the Wilcoxon rank sum test.

Therefore, the procedure produces a valid p-value regardless of whether the proportional odds model is correct. Nonetheless, estimation and confidence intervals do require the model to be correct. Accordingly, we will evaluate model fit using a goodness-of-fit likelihood ratio test. A stratified hypothesis test to account for baseline severity of disease will be used.

The distribution of severity results will be summarized by treatment arm as percentages. The validity of the proportionality assumption will be evaluated and tested. Efforts to minimize loss-to-follow-up will be considerable. However, small amounts of missing data may occur. In such cases, participants without final outcome data will be excluded from the analysis. Sensitivity analyses will evaluate the impact of making different assumptions about missing observations. These sensitivity analyses will be fully defined in the SAP.

### **12.4 Analysis of the Secondary Endpoint(s)**

1. Differences in time-to-event endpoints (e.g., time to a one category improvement in ordinal scale) by treatment will be summarized with Kaplan-Meier curves and 95% confidence bounds.
2. Change in ordinal scale at specific time points will be summarized by proportions (e.g., proportion who have a 1-, 2-, 3-, or 4-point improvement or 1-, 2-, 3-, 4-point worsening).
3. Duration of event (e.g., duration of mechanical ventilation) will be summarized according to median days with quartiles.
4. Incidence data (e.g., incidence of new oxygen use) will be summarized as a percent with 95% confidence intervals.
5. Categorical data (e.g., 14-day mortality or ordinal scale by day) will be summarized according to proportions with confidence intervals on the difference or odds ratios for a binary or multiple category scale, respectively.

Missing data procedures will be described in the SAP.

### **12.5 Safety Analyses**

Safety endpoints include death through Day 14 or 28, SAEs, discontinuation of study infusions, and severe AEs. These events will be analysed univariately and as a composite endpoint. Time-to-event methods will be used for death and the composite endpoint. Each AE will be counted once for a given participant and graded by severity and relationship to COVID-19 or study intervention. AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by system organ class, duration (in days), start- and stop-date. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs should be presented either in a table or a listing.

### **12.4.5 Baseline Descriptive Statistics**

Baseline characteristics will be summarized by treatment arm. For continuous measures the mean and standard deviation will be summarized. Categorical variables will be described by the proportion in each category (with the corresponding sample size numbers).

### **12.7 Planned Interim and Early Analyses**

#### Early analyses

An initial blinded endpoint-evaluation phase will be enrolled prior to specification of the primary endpoint. Analysis and decision making will be restricted to a blinded endpoint evaluation committee (a BEEC). BEEC membership will be defined elsewhere and will consist only of individuals who are blinded to treatment assignment. Principles of blinded endpoint-evaluation will be defined in a separate document.

Additional early analyses include monitoring enrolment, baseline characteristics, and follow-up rates throughout the course of the study by the study team. Analyses will be conducted blinded to treatment assignment.

#### Interim analyses

A DSMB will monitor ongoing results to ensure patient well-being and safety as well as study integrity. The DSMB will be asked to recommend early termination or modification only when there is clear and substantial evidence of a treatment difference. More details about the interim analyses are described in section **Error! Reference source not found.** and **Error! Reference source not found.** below as well as DSMB Charter.

###### ***Interim Safety Analyses***

Interim safety analyses will occur at approximately 25%, 50%, and 75% of total enrolment. Safety analyses will evaluate serious AEs by treatment arm and test for differences using a Pocock spending function approach with a one-sided type I error rate of 0.025. This approach is less conservative than what will be used to test for early efficacy results because proving definitive harm of the experimental agents is not the focus of this study. Pocock stopping boundaries at the looks described correspond to z-scores of (2.37, 2.37, 2.36, & 2.35). This contrasts with the z-score stopping boundaries for the Lan-DeMets spending function that mimics O’Brien-Fleming boundaries: (4.33, 2.96, 2.36 & 2.01). The unblinded statistical team will prepare these reports for review by the DSMB.

###### ***Interim Efficacy Review***

The Lan-DeMets spending function analog of the O’Brien-Fleming boundaries will be used to monitor the primary endpoint as a guide for the DSMB for an overall two-sided type-I error rate of 0.05. Interim efficacy analyses will be conducted after the BEEC has selected the primary efficacy endpoint at approximately 50%, 75% and 100% of total information.

Conditional power will be presented as an additional guide to the DSMB. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the trial given the data accumulated thus far, incorporating and assuming a hypothesized treatment effect (e.g., the treatment effect assumed for sample size determination) thereafter. If conditional power is less than 20% under the original trial assumptions, consideration should be given to stopping the trial.

The unblinded statistical team will prepare these closed reports for DSMB review and recommendations. Analyses will be presented with blinded codes for treatment arms to protect against the possibility that the DSMB report may fall into the wrong hands. A DSMB charter will further describe procedures and membership. An additional document on statistical issues related to monitoring will be provided to the DSMB prior to interim analyses.

### **12.8 Sub-Group Analyses**

Subgroup analyses for the primary outcomes will evaluate the treatment effect across the following subgroups: geographic region, duration of symptoms prior to enrolment, age and sex. A forest plot will display confidence intervals across subgroups. Interaction tests will be conducted to determine whether the effect of treatment varies by subgroup.

# **13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

## Regulatory, Ethical, and Study Oversight Considerations

This study will be conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research and the ICH E6(R2) as well as the NMRA requirements in each country.

The IRB will review and approve this protocol, associated informed consent documents, recruitment material and mechanism, and hand outs or surveys intended for the study participants prior to the recruitment, screening, and enrolment of subjects. Site IRB may have additional national and local regulations.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the duration of the study. The investigator will notify the IRB of deviations from the protocol and SAEs, as applicable to the IRB policy.

DSMB must receive the documentation that verifies IRB-approval for this protocol, informed consent documents, and associated documents prior to the recruitment, screening, and enrolment of subjects, and any IRB-approvals for continuing review or amendments as required by the DSMB.

### **13.1.1 Informed Consent Process**

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual’s trial participation. Investigators or designated research staff will obtain a subject’s informed consent in accordance with the requirements of 45 CFR 46, 21 CFR 50 and 21 CFR 56 for FDA-regulated studies, state and local regulations and policy, and ICH E6 GCP before any study procedures or data collection are performed.

Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent form. The key information about the study will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate. A sample of informed consent for this study will be included in the Investigator’s Brochure (IB) as an Annex.

ICFs will be IRB-approved, and subjects will be asked to read and review the consent form. Subjects (or legally authorized representatives) must sign the ICF prior to starting any study procedures being done specifically for this trial. Once signed, a copy of the ICF will be given to the subject for their records.

New information will be communicated by the site PI to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated, and subjects will be re-consented per IRB requirements, if necessary.

Further details are described in the SOPs.

#### Other Informed Consent Procedures

Participants will be asked for consent to collect additional blood, the use of residual specimens, and samples for secondary research. Extra blood will be drawn for secondary research during each visit when a study blood samples are obtained.

The stored samples will be labeled with barcodes to maintain confidentiality. Research with identifiable samples and data may occur as needed, however, subject confidentiality will be maintained as described for this protocol and with IRB approval.

Samples designated for secondary research use may be used for understanding the SARS-CoV-2 infection, the immune response to this infection, and the effect of therapeutics on these factors.

Samples will not be sold for commercial profit. Although the results of any future research may be patentable or have commercial profit, subjects will have no legal or financial interest in any commercial development resulting from any future research.

There are no direct benefits to the subject for extra specimens collected or from the secondary research. No results from secondary research will be entered into the participant’s medical record. Incidental findings will not be shared with the subject, including medically actionable incidental findings, unless required by law.

Participants may withdraw permission to use samples for secondary use at any time. They will need to contact the study site and the samples will be removed from the study repository after this study is completed and documentation will be completed that outlines the reason for withdrawal of permission for secondary use of samples.

### **13.1.2 Study Termination and Closure**

In Section 10.1.4 above, Study Intervention Discontinuation and Subject Discontinuation/Withdrawal, describes the temporary halting of the study.

This study may be prematurely terminated if there is sufficient reasonable cause, including but not limited to:

* Determination of unexpected, significant, or unacceptable risk to subjects
* Results of interim analysis
* Insufficient compliance to protocol requirements
* Data that are not sufficiently complete and/or not evaluable
* Regulatory authorities

If the study is prematurely terminated, the site PI will promptly inform study subjects and the IRB as applicable. The site PI will assure appropriate follow-up for the subjects, as necessary. The sponsor will notify the NMRA and the DSMB.

### **13.1.3 Confidentiality and Privacy**

Participant’s confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover clinical information relating to subjects, test results of biological samples and genetic tests, and all other information generated during participation in the study. No identifiable information concerning subjects in the study will be released to any unauthorized third party. Participant’s confidentiality will be maintained when study results are published or discussed in conferences.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All source records including electronic data will be stored in secured systems in accordance with institutional policies and federal regulations.

All study data and research specimens that leave the site (including any electronic transmission of data) will be identified only by a coded number that is linked to a subject through a code key maintained at the clinical site. Names or readily identifying information will not be released and it aligns with the consent form, or according to laws for required reporting.

### **13.1.4 Secondary Use of Stored Specimens and Data**

Secondary Human Subject Research is the re-use of identifiable data or identifiable biospecimens that were collected from some other ‘‘primary’’ or ‘‘initial’’ activity, such as the data and samples collected in this protocol. Any use of the sample or data for secondary research purposes, however, will be presented in a separate protocol and require separate IRB approval.

Each sample will be labelled only with a barcode and a unique tracking number to protect subject confidentiality. Secondary research with coded samples and data may occur, however, subject confidentiality will be maintained as described for this protocol. An IRB review of the secondary research using coded specimens is required.

The participant’s decision can be changed at any time by notifying the study doctors or nurses in writing. If the subject subsequently changes his/her decision, the samples will be destroyed if the samples have not been used for research or released for a specific research project.

### **13.1.5 Data Sharing for Secondary Research**

Data from this study may be used for secondary research. All of the individual subject data collected during the trial will be made available after de-identification. The SAP and Analytic Code will also be made available. This data will be available immediately following publication, with no end date.

The investigator may request removal of data on individual study subjects from NIH data repositories in the event that a research subject withdraws or changes his or her consent. However, some data that have been distributed for approved research use cannot be retrieved.

## 13.2 Key Roles and Study Governance

The study may be sponsored by the Government. , an institution, or the private sector. Decisions related to the study will be made by research team at each site which will be reviewed by the DSMB. The final recommendations regarding the clinical outcomes of the trial is the responsibility of the DSMB.

###  **Safety Oversight**

#### Protocol team oversight

The protocol team will review blinded pools of AE data every 2 weeks to ensure there no significant number of unexpected AEs (AEs that do not fit with the known course of COVID-19). If there are a significant number of unexpected AEs, the DSMB will be asked to review unblinded safety data in an ad hoc meeting.

#### Data Safety Monitoring Committee

Safety oversight will be conducted by the DSMB. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial.

The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial. The DSMB should be as broadly informed as possible regarding emerging evidence from related studies as well as from the conduct of this Master Protocol. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DSMB will review SAEs on a regular basis and ad hoc during this trial.

The DSMB will conduct the following reviews:

* After every 50 subjects are dosed.
* Ad hoc meeting if the protocol team raises any concerns
* A final review meeting after final clinical database lock, to review the cumulative unblinded safety data for this trial.

The study will not stop enrolment awaiting these DSMB reviews, though the DSMB may recommend temporary or permanent cessation of enrolment based on their safety reviews.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion and may request the treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study interventions (as applicable), and to continue, modify, or terminate this trial.

### **Clinical Monitoring**

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable. Clinical monitoring also ensures conduct of the trial is in compliance with the currently approved protocol/ amendment(s), ICH, GCP, and with applicable regulatory requirement(s) and sponsor requirements. Clinical monitoring will also verify that any critical study procedures are completed following specific instructions in the protocol-specific SOP.

Monitoring for this study will be performed by the DSMB. Details of clinical site monitoring are documented in a clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, CRFs, ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the SOPs. Study monitors will meet with site PIs to discuss any problems and outstanding issues and will document site visit findings and discussions.

### **Data Handling and Record Keeping**

#### Data Collection and Management Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site PI. The site PI must maintain complete and accurate source documentation.

Clinical research data from source documentation (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, clinical laboratory data) will be entered by the clinical study site into CRFs via a 21 CFR Part 11-compliant internet data entry system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. AEs and concomitant medications will be coded according to the most current versions of MedDRA and WhoDrug, respectively.

The DSMB for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

The IND sponsor is responsible for review of data collection tools and processes, and review of data and reports.

AEs will be coded according to the MedDRA dictionary version 23.0 or higher.

A separate study specific Study Data Standardization Plan (SDSP) appendix will be developed which describes the technical recommendations for the submission of human study data and related information in a standardized electronic format throughout product development.

At the end of the study, a copy of all datasets including annotated CRFs and data dictionary will be provided to the DSMB.

#### Study Record Retention

Study related records, including the regulatory file, study product accountability records, consent forms, subject source documents and electronic records should be maintained for a period of 2 years following the date a marketing application is approved for herbal medicine for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. These documents should be retained for a longer period, however, if required by local policies or regulations. No records will be destroyed without the written consent of DMID. Consent forms with specimen retention linked to identifiable specimens will be maintained for as long as the specimens remain in identifiable format, and a minimum of three years after use of the identifiable specimens in non-exempt human subject research.

#### Source Records

Source data are all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH GCP, regulatory, and institutional requirements. Data recorded in the CRF derived from source documents should be consistent with the data recorded on the source documents.

Interview of subjects is sufficient for obtaining medical history. Solicitation of medical records from the subject’s primary care provider is not required.

###  **Protocol Deviations**

A protocol deviation is any noncompliance with the clinical trial protocol, any process that is noted in the protocol and refers to details in the protocol-specific SOPs.

The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Following a deviation(s), corrective actions should be developed by the site and implemented promptly. All individual protocol deviations will be addressed in participant study records.

It is the responsibility of the site PI and personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported per the protocol deviation reporting procedures. Protocol deviations must be sent to the local IRB/NMRA per their guidelines. The site PI and personnel are responsible for knowing and adhering to their IRB requirements. A completed copy of the Protocol Deviation Form must be maintained in the Regulatory File, as well as in the subject’s chart if the deviation is subject specific.

### **Publication and Data Sharing Policy**

The members of the research team will discuss with the Sponsor of the Trial on publication policy. The Final Study Report will be prepared by the principal investigator and co-investigators and signed by the PI. Any publication related to the study must be approved by the sponsor before submission of the manuscript. All the study investigators must have the opportunity to review the proposed abstract, manuscript or presentation before submission for publication. Any information identified as confidential must be deleted prior to submission for publication. The persons identified as authors of the publication(s) are those who have contributed to the development and/or execution of the protocol, and/or to the analysis of the data, drafting and reviewing the manuscript.

### **Conflict of Interest Policy**

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. DMID has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

**13.2.7. Intellectual Property Rights (IPR).**

## The ownership of the IPR will be treated in accordance with the practice in the country.

# **14**. **ADDITIONAL CONSIDERATIONS**

## *Research Related Injuries*

For any potential research related injury, the site PI or designee will assess the subject.

Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating study site.

As needed, referrals to appropriate health care facilities will be provided to the subject. The site PI should then determine if an injury occurred as a direct result of the tests or treatments that are done for this trial.

If it is determined by the participating site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject.

Study personnel will try to reduce, control and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions.

## *Insurance Claims*

Liability and compensation in cases of SAEs will be treated in accordance with applicable national health insurance policies of the participating countries.

**15. FINAL REPORT**

The final report shall consist of summary of the work done, introduction, materials and methods, results and discussion section. The observations and comments made by the independent quality assurance scientist shall be noted in the Report. The final report must be signed by the Principal Investigator (PI).

**16. ARCHIVING**

The clinical trial data will be stored at the IMRA for at least a period of 15 years as specified by NMRA

**17. CASE RECORD FORMS (CRFS)/DATA COLLECTION FORMS**

The following forms should be generated before commencement of the study. Templates of these CRFs are contained in the Investigators’ Brochure which can be adapted/adopted by each research team in accordance with the national regulations.

* + Schedule of visits
	+ Personal data
	+ Prior history
	+ Physical examination/vital signs and symptom monitoring
	+ Cardiac study, chest x-ray and ophthalmology review
	+ Haematological monitoring
	+ Biochemistry monitoring
	+ Microbiology monitoring
	+ Adverse experiences/concomitant treatment

**PROTOCOL AMENDMENT HISTORY**

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| --- | --- | --- | --- |
| **Version**  | **Date** | **Description of change** | **Brief Rationale** |
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